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02018229.1 21 August 2002 (21.08.2002) EP
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- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/018684 A3

(54) Title: T-CELL EPITOPES IN STAPHYLOCOCCAL ENTEROTOXIN B

(57) Abstract: The present invention relates to the field of immunology. The invention identifies determinants on staphylococcal enterotoxin B (SEB) able to evoke an immune response. In particular the invention is concerned with the identification of epitopes for T-cells in SEB. The invention relates furthermore to T-cell epitope peptides derived from SEB by means of which it is possible to create modified SEB variants with reduced immunogenicity.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P02/131-bzgs	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 03/09116	International filing date (day/month/year) 18/08/2003	(Earliest) Priority Date (day/month/year) 21/08/2002
Applicant MERCK PATENT GMBH		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
 - b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :
 - contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished
2. Certain claims were found unsearchable (See Box I).
3. Unity of invention is lacking (see Box II).
4. With regard to the title,
 - the text is approved as submitted by the applicant.
 - the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/09116

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 4 and 6-8 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 4 and 6-8

Present Claim 4 and, as far as they depend on said claim, Claims 6-8 relate to an extremely large number of possible compounds. In fact, the claims contain so many possible permutations that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear, namely the molecule of Claim 5.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/09116

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C12N15/31 C07K14/31 A61K39/085 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X 	<p>DATABASE BIOSIS 'Online!' BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; March 2001 (2001-03), YU HONG ET AL: "Study on expression and functions of staphylococcal enterotoxin B mutants" XP002274645 Database accession no. PREV200100232318 abstract & ZHONGHUA WEISHENGWUXUE HE MIANYIXUE ZAZHI, vol. 21, no. 2, March 2001 (2001-03), pages 200-205, ISSN: 0254-5101</p> <p>-----</p> <p style="text-align: center;">-/--</p>	1-14

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

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27 May 2004

07.06.2004

Name and mailing address of the ISA
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Mata Vicente, T.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/09116

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ②	KAPPLER J W ET AL: "MUTATIONS DEFINING FUNCTIONAL REGIONS OF THE SUPERANTIGEN STAPHYLOCOCCAL ENTEROTOXIN B" JOURNAL OF EXPERIMENTAL MEDICINE, TOKYO, JP, vol. 175, February 1992 (1992-02), pages 387-396, XP002920019 ISSN: 0022-1007 page 391; figure 2	1-14
X ⑧	HAYBALL JOHN D ET AL: "Identification of two binding sites in staphylococcal enterotoxin B that confer specificity for TCR V-beta gene products" INTERNATIONAL IMMUNOLOGY, vol. 6, no. 2, 1994, pages 199-211, XP0008028595 & ISSN: 0953-8178 abstract	1-14
X ③	PANG LIWINA T Y ET AL: "Inhibition of staphylococcal enterotoxin B-induced lymphocyte proliferation and tumor necrosis factor alpha secretion by MAbs, an anti-toxic shock syndrome toxin 1 monoclonal antibody" INFECTION AND IMMUNITY, vol. 68, no. 6, June 2000 (2000-06), pages 3261-3268, XP002274643 & ISSN: 0019-9567 abstract	9-14
X ④	WEN RENREN ET AL: "The conventional CD4+ T cell response to staphylococcal enterotoxin B is modified by its superantigenic activity" CELLULAR IMMUNOLOGY, vol. 176, no. 2, 1997, pages 166-172, XP002274644 & ISSN: 0008-8749 figure 2B	9-14
X ⑤	SOOS J M ET AL: "Multiple binding sites on the superantigen, staphylococcal enterotoxin B, imparts versatility in binding to MHC class II molecules" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 201, no. 2, 15 June 1994 (1994-06-15), pages 596-602, XP002253159 ISSN: 0006-291X page 600, last paragraph page 599, paragraph 2	9-16

INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X <i>(9)</i>	REECE J C ET AL: "Mapping the major human T helper epitopes of tetanus toxin. The emerging picture" JOURNAL OF IMMUNOLOGY, THE WILLIAMS AND WILKINS CO. BALTIMORE, US, vol. 151, no. 11, 1 December 1993 (1993-12-01), pages 6175-6184, XP002269741 ISSN: 0022-1767 page 6175, right-hand column, paragraph 1 -----	15, 16
X <i>(10)</i>	LAUNOIS P ET AL: "T-CELL-EPITOPE MAPPING OF THE MAJOR SECRETED MYCOBACTERIAL ANTIGEN AG85A IN TUBERCULOSIS AND LEPROSY" INFECTION AND IMMUNITY, AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON, US, vol. 62, no. 9, 1 September 1994 (1994-09-01), pages 3679-3687, XP000572211 ISSN: 0019-9567 abstract -----	15, 16
A <i>(6)</i>	BAVARI S ET AL: "ENGINEERED BACTERIAL SUPERANTIGEN VACCINES" VACCINES, XX, XX, vol. 96, 1995, pages 135-141, XP000916124 the whole document -----	1-14
A <i>(7)</i>	WO 00/09154 A (BAVARI SINA ; OLSON MARK A (US); ULRICH ROBERT G (US); WALTER REED ARM) 24 February 2000 (2000-02-24) page 3, line 17 - page 4, line 24 -----	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/09116

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 0009154	A.	24-02-2000	WO 0009154 A1	24-02-2000
			AU 762813 B2	03-07-2003
			AU 8904998 A	06-03-2000
			CA 2338184 A1	24-02-2000
			EP 1105154 A1	13-06-2001
			JP 2002522055 T	23-07-2002

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(74) Common Representative: MERCK PATENT GMBH; Frankfurter Strasse 250, 64293 Darmstadt (DE).

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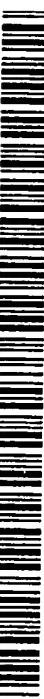
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(71) Applicant (*for all designated States except US*): MERCK PATENT GMBH [DE/DE]; Frankfurter Strasse 250, 64293 Darmstadt (DE).

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